PARASITE PHYSIOLOGY

Trypanosomes chew the fat

Trypanosoma brucei is an extracellular protozoan parasite that is the causative agent of human African trypanosomiasis, a frequently fatal disease that is commonly known as sleeping sickness. The life cycle of *T. brucei* involves infection of the vector, the tsetse fly, and transmission to the blood of mammalian hosts through the bite of the fly. Two major niches have been described for *T. brucei* in mammalian hosts: the blood and, after crossing the blood–brain barrier, the central nervous system. However, Trindade *et al.* now show that adipose tissue is a third major niche for *T. brucei* in mammalian hosts and, furthermore, that the parasite may use the fatty acids that are present in this tissue as a carbon source.

Immunohistochemistry of mice that were infected with *T. brucei* showed that, in addition to blood, parasites are present in the interstitial space of several organs, including adipose tissue. A quantitative comparison, based on the amount of parasite DNA, showed that the parasite density in adipose tissue was only seven-times lower than in blood at 6 days post-infection, and sixty-times higher than in other organs. The parasite density in blood decreased during the course of infection; however, the parasite density in adipose tissue remained constant, such that by 28 days post-infection adipose tissue was the site of highest parasite density, which corresponded to a total parasite load that was higher in adipose tissue than in all other sites combined. Thus,

adipose tissue is a novel niche that is occupied by *T. brucei* during the infection of mammalian hosts.

In the early stages of mammalian infection, *T. brucei* adopts a morphologically ‘slender’ form, which is replicative, whereas during the later stages of infection slender parasites can differentiate into a morphologically ‘stumpy’ form, which is growth-arrested. Using a fluorescent marker of a developmental gene, the authors tracked the distribution of developmental stages of the parasite in the mouse model. At 4 days post-infection, 98% of parasites in the blood remained in the slender form, whereas at 6 days post-infection, 86% of parasites in the blood were differentiated into the stumpy form or, more rarely, a developmentally intermediate form. Adipose tissue also contained a mixed population of these three developmental stages, as was confirmed by morphological examination. However, only 21% of parasites in adipose tissue were differentiated into stumpy or intermediate forms at 6 days post-infection. Cell-cycle analysis and the injection of adipose tissue into naive mice demonstrated that parasites in adipose tissue remain competent for replication and infection.

Finally, comparative analysis of the transcriptomes of parasites in the blood and parasites in adipose tissue revealed the differential expression of many genes with functions in metabolic pathways, which suggests that *T. brucei* may adapt its metabolism to the energy sources that are present

Trypanosoma brucei. Image courtesy of T. Carvalho and A. L. Pinto, Universidade de Lisboa, Portugal.

in adipose tissue, notably fatty acids. Indeed, of particular interest was the upregulation of genes with functions in the β -oxidation of fatty acids, as this metabolic pathway is not active in *T. brucei* in other niches. Pulse-chase experiments using radiolabelled myristate as a fatty acid confirmed that the fatty acid β -oxidation pathway was active in parasites from adipose tissue but not from blood. Prompted by this finding, the authors note that an aetiologically unexplained symptom of sleeping sickness is weight loss, and speculate that the metabolism of fatty acids by parasites in adipose tissue might contribute to weight loss in infected individuals.

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